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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/447,681	11/23/1999	JACK A. ROTH	INRP.003--2/	4103

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EXAMINER
CROUCH, DEBORAH

ART UNIT	PAPER NUMBER
1632	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/447,681	Applicant(s) ROTH, JACK A.	
	Examiner Deborah Crouch	Art Unit 1632	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *13* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *detailed action* .

Applicant's arguments filed Nov. 27, 2001 in paper no. 15 have been fully considered but they are not persuasive. The declaration by Louis Zumstein, Ph.D. has been fully considered, but not found persuasive with regard to the written description rejection as discussed below.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 67 remains provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 22,29 and 32-34 of copending Application No. 09/668,532 for reasons of record as set forth in the office action mailed April 18, 2001, paper no. 12.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The rejection is maintained for reasons of record as set forth in the office action mailed April 18, 2001, paper no. 12. Applicant has not submitted arguments as to why the rejection is improper, but has indicated a willingness to filed a terminal disclaimer if appropriate.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 67 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for reasons of record as set forth in the office action mailed April 18, 2001, paper no. 12.

Applicant argues the specification describes the claimed invention clearly enough to permit the ordinary artisan to recognize that they had possession of the claimed invention at the time of filing. Applicant notes that the subject matter of the claim is not required to be literally described. Applicant then points to specific passages in the specification that they contend provides written description of the invention. Applicant argues that by reading the passages the ordinary artisan would combine individual contemplations to arrive at the claimed invention. Declarant Zumstein states that he is familiar with the level of skill of scientists working the field of gene therapy at the priority date, October, 1992 of the present application. These arguments by applicant and statements by declarant are not persuasive as there is no direction in the specification to combine the separate teachings in the art.

MPEP 2163.02 states:

> Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., Pfaff v. Wells Electronics, Inc., 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); Regents of the University of California v. Eli Lilly, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); Amgen, Inc. v. Chugai Pharmaceutical, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it"). The subject matter of the claim need not be described literally (i.e., using the same terms or in haec verba) in order for the disclosure to satisfy the description requirement. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

It is maintained that the present specification provides no such reasonable clarity to those skilled in the art that applicant was in possession of the claimed invention. With regard to applicant's arguments concerning the passage at page 8, line 25 to page 9, line for, a fair reading of this passage indicates that it

contemplates the insertion of the promoter/gene construct in reverse orientation with respect to other promoters in the vector. In particular the contemplation is that in retroviral vector the promoter/gene is placed in opposite orientation to the expression direction of the LTR's. However, this is not a possible description of adenovirus as not all adenovirus promoters express in the same direction. Thus it would be impossible to construct an adenovirus where the CMV promoter/p53 gene construct would be in reverse orientation of adenovirus promoters. Thus, the claimed adenovirus has no support at this passage. At the passage, page 14, lines 21-23, the term adenovirus does appear, but a full reading of the passage indicates that adenovirus will not fulfill the requirements of the vector because 1) adenovirus unlike retrovirus does not integrate in the infect cell's genome (lines 12-14), and 2) the claimed invention is an adenovirus comprising a p53 gene and not an antisense sequence (lines 17-21). When reading the paragraph from which the passage is derived, one sees that the contemplation is that the virus contain an antisense sequence and that the virus integrate into the genome. A combination of either of these two passages with that cited as page 16, lines 5-10, does not provide the missing support. The paragraph states "[w]hile the retroviral construct aspect of the present invention concerns the use of β-action promoter in reverse orientation, there is no limitation on the nature of the selected gene which one desired to have expressed. Thus, the invention concerns the use of antisense-encoding constructs as well as "sense" constructs that encode a desired protein." This passage/paragraph states that it contemplated for retroviral vectors to use the β-actin promoter in reverse orientation to the endogenous retroviral promoters (LTR's) and have the expression of either sense or antisense sequences from that β-actin promoter. As stated in the previous office action, page 15, lines 1-5 states that "while the β-actin promoter is preferred in the invention is by no means limited to this promoter, and one may also mention .....CMV." However, when the entire paragraph is read, "the invention" at this point is the expression of antisense sequences. Please refer to the paragraph at page 14, line 27 "the particular promoter that is employed to control the expression of the antisense RNA in a vector construct is not believed to be particularly crucial ..... where a human cell is targeted, it will be preferred to position the antisense RNA coding region adjacent to and under the control of a promoter that is capable of being expressed in a

human cell ... generally speaking, such a promoter might include either a human cellular or viral promoter..... while the β-actin promoter is preferred .... CMV". A reading of the complete paragraph assigns the citation provided by applicant to refer only to retrovirus vectors expressing antisense.

The Zumstein declaration is not persuasive as the passages quoted clearly do not contemplate even figuratively the claimed adenovirus comprising a CMV promoter operatively linked to a p53 gene. The passaged referred to, page 6, lines 33-35 states "another important oncogene is the gene encoding the p53 cellular protein". The paragraph goes on to discuss the role of p53 mutations in the development of lung cancer. On page 7, line 14, it is stated "one approach that has been suggested as a means of treatment ... is the introduction of so-called 'wild-type' or non-mutated p53 ... through the use of retroviral vectors. As stated above, at the passage, page 14, lines 22-23, the term adenovirus does appear, but a full reading of the passage indicates that adenovirus will not fulfill the requirements of the vector because 1) adenovirus unlike retrovirus does not integrate in the infect cell's genome (lines 12-14), and 2) the claimed invention is an adenovirus comprising a p53 gene and not an antisense sequence (lines 17-21). As stated in the previous office action, page 15, lines 1-5 states that "while the β-actin promoter is preferred in the invention is by no means limited to this promoter, and one may also mention .....CMV." However, when the entire paragraph is read, "the invention" at this point is the expression of antisense sequences. Please refer to the paragraph at page 14, line 27 "the particular promoter that is employed to control the expression of the antisense RNA in a vector construct is not believed to be particularly crucial ..... where a human cell is targeted, it will be preferred to position the antisense RNA coding region adjacent to and under the control of a promoter that is capable of being expressed in a human cell ... generally speaking, such a promoter might include either a human cellular or viral promoter..... while the β-actin promoter is preferred .... CMV". A reading of the complete paragraph assigns the citation provided by applicant to refer only to retrovirus vectors expressing antisense. Thus a full reading of the cited passages provides reasoning to disagree with the conclusion of declarant Zumstein.

Neither applicant's arguments nor the statements by the declarant provide the reasonable clarity required for the specification to meet the written description requirements of claim 67.

Claims 67 remains rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons of record as set forth in the office action mailed April 18, 2001, paper no. 12.

The specification fails to enable the claimed invention as the specification does not provide a source for packaging cell lines for the production of adenoviral vectors that contain the p53 gene in a region of the adenoviral genome essential for replication. It is noted that at the time of filing, 293 cells were known that packaged adenoviral vectors, but only those vectors with a defective E1a region. As for other regions necessary for adenoviral packaging, E2 and E4, the specification nor the art provide a source for packaging cells that complement deletions of this region. Without knowledge of packaging cell lines which complement vectors having E2 and E4 deletions, the bread of the claimed invention is not enabled.

The rejection regarding E2B binding wild-type 53 is overcome by applicant's explanation.

With regard for the need of adenoviral packaging cells to produce virus as claimed for the entire breadth of the claim, applicant argues that to produce a complementing or packaging cell line for an adenovirus containing a deletion in a region other than E1 would not have required undue experimentation. Applicant argues that adenoviral vectors comprising an E3 deletion were known. Applicant argues that the existence of E3 deletion virus shows that some experimentation might be required to generate deletions in other regions and develop complementing cell lines to propagate virus, it would not require undue experimentation. These arguments are not persuasive.

First, E3 is not required for, much less essential for, adenovirus replication. Thus, E3 complementing packaging cells are not required for produced E3 deleted adenovirus. Jaffe (Appendix D) does not mention the need for E3 complementing cell lines, although Jaffe does disclosed E1-E3- adenovirus. More likely than not, the AdE1-E3- adenovirus of Jaffe were produced in 293 cells which provide E1.

To further rebut applicant's statements that the production of complementing cells lines for adenovirus deleted in other essential regions, the following argument is present.

At the time of filing, a summary of the relevant art taught that complementing or packaging cell lines for other than adenovirus E1- were not in use (U.S. Patent 5,994,106), which states "[u]ntil now, adenoviral vectors used to express a foreign gene have been deficient only for a single early region (E1), that is essential of viral growth .... only the essential region E1 or, alternatively, the nonessential region E3 has been removed ... (col. 4, lines 57-62). This statement is made in view of the fact that complementing cell lines were known for singly defective viruses (U.S. Patent 5,994,106, col. 5, lines 2-4). The teachings of '106 indicate that these known cells lines, with the state exception of E1- adenovirus, were not accepted by the art for use in producing adenovirus singly defective vectors. Further, it was know at the time of filing that the 293 cells approach to delete adenovirus gene sequences required for virus replication and develop a cell line that complements the required functions of the deleted region in trans (Armentano, page 1344, col. 1, parag. 1, lines 3-7). This method was problematic due the large number of structural and regulatory genes, many of which are temporally regulated, function stoichiometrical, and maybe toxic to cells at levels required for complementation (Armentano, 1344, col. 1, parag. 1, lines 9-11). These statement are made in view of the fact that modestly E2 and E4 complementing cell lines were known (Armentano, page 1344, col. 1, parag. 1, lines 13-16). In addition, Armentano states that the production of 293 cells was difficult and other E1 complementing cell lines are few if any (Armentano, page 1344, col. 1, parag. 1, lines 7-9). These cited teachings provide support that complementing cell lines for singly, much less multiply deleted adenoviruses were unpredictable at the time of filing. The specification does not overcome this lack of teaching in the art by providing for such cell lines. In fact the specification does not teach what type of adenovirus is to be used as vector. There is no disclosure at to the virus being E1, E2, E3, E4 and/or other deletions.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject

> matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 67 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al (1990) Science 250, 1576-1579 in view of Colicos et al (1991) Carcinogenesis 12, 249-255 further in view of Pasleau et al (1985) Gene 38, 227-232 for reasons of record as set forth in the office action mailed April 18, 2001, paper no. 12..

Claim 67 is drawn to an adenovirus vector comprising a wild type p53 gene under the control of a CMV promoter.

Applicant argues that there is no suggest to combine the cited reference to reach the claimed invention, claim 67. Applicant argues that Chen says nothing about adenovirus and nothing about CMV promoters. Applicant argues that Colicos says nothing about tumor suppressors or about p53, but specifically state that adenovirus can be used to study the expression of DNA repair genes in untransformed mammalian cell types. Applicant argues that Chen uses transformed cells while Colicos uses nontransformed cells. Applicant argues that Pasleau does not suggest nor provide motivation for an adenoviral vector comprising wild type p53 under the control of a CMV promoter. Applicant argues that just because references can be combined doesn't mean that they can (legally) be combined. These arguments are not persuasive.

As motivation is the crux of applicant's arguments, the motivation statements from the previous obviousness rejection are repeated here. A motivation statement was provided for each of the three references, and these statements all lead the ordinary artisan to the claimed inventions.

> Motivation is provided by Chen et al in stating that expression of p53 in Saos cells which lack functional p53 reverts the transformed phenotype (page 1579, col. 1, parag. 1, line 1 to col. 2, line 1). Colicos et al further provides motivation by teaching that adenovirus was selected as it has a broad host range, making it a suitable vector for the study of mammalian gene expression (page 249, col. 2, parag. 3, lines 5-9). Pasleau also offers motivation for the substitution of the CMV promoter for the RSV LTR in stating that the CMV promoter led to the synthesis of three to five times more bGH that the RSV LTR (page 231, col. 1, parag. 1, lines 4-9).

The motivation provided by Chen was to use a vector comprising p53 to revert the transformed phenotype, the motivation to use Colicos was that adenovirus has a broad host range for the study of

mammalian gene expression and the motivation to use Pasleau was that the CMV promoter had exhibited strong expression levels. The reason for using Chen was for p53 as a reverser of transformation, for Colicos was for the use of adenovirus, and Pasleau the CMV promoter. The motivation is clear. Applicant has not explained the exact reasoning as to why this motivation is faulty. Mere statements of no motivation is not sufficient Applicant needs to explain why.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

The fax number is (703) 308-4242.

Deborah Crouch

DEBORAH CROUCH
PRIMARY EXAMINER
GROUP 1800/1630

Dr. D. Crouch
February 8, 2002